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(54) Title: PHARMACEUTICAL COMBINATIONS

(57) Abstract: The present invention provides novel pharmaceutical combinations and their use in anti-thrombotic therapy.

# PHARMACEUTICAL COMBINATIONS

## FIELD OF THE INVENTION

The present invention relates to pharmaceutical combinations comprising a $P_{2T}$ receptor antagonist and another anti-thrombotic agent and to their use in the treatment and prevention of thrombosis.

## BACKGROUND OF THE INVENTION

Increased understanding of the mechanisms underlying thrombosis and of interventions therein has led to a polypharmacological anti-thrombotic approach utilising appropriate combinations of anti-platelet, anti-coagulant and fibrinolytic agents. Examples of anti-thrombotic compounds used include anti-platelet agents such as aspirin, clopidogrel, ticlopidine, GPIIb/IIIa antagonists; anti-coagulants such as thrombin inhibitors, warfarin, heparin and low molecular weight heparins; and fibrinolytic agents including but not limited to, streptokinase, tissue plasminogen activator (tPA) and tenecteplase.

Most patients with acute myocardial infarction are currently treated using either a thrombolytic agent or intervention treatment with percutaneous coronary angioplasty (PTCA). It has been shown that the use of both these methods result in an increase in the number of patients achieving acceptable coronary artery patency at 90 minutes, and that the better the flow in the affected coronary artery, the greater the survival.

However, even the most effective thrombolytic agents with adjunctive aspirin and heparin treatment are only moderately effective in achieving coronary artery patency with normal blood flow (assessed as TIMI grade 3) in about 50% of cases. In addition, in the acute setting where immediate effect is paramount, slow-acting agents leave a window where the patient is not protected from thrombosis. For example, clopidogrel inhibits ADP-induced platelet aggregation and, like the earlier analogue, ticlopidine, has shown clinical efficacy in arterial thrombosis. However, both agents produce incomplete, slow to develop

inhibition of the ADP response, properties which are far from ideal in acute therapy, such as prevention of stent occlusion, although increasing use of a loading dose has been a recent advance.

Another short-coming of existing anti-thrombotic agents, and combinations thereof, is that the optimal pharmacodynamic risk:benefit (anti-thrombotic:anti-haemostatic) relationship has not yet been achieved.

Thus there is a need for more effective anti-thrombotic therapy.

Recently it has been shown that $P_{2T}$ (also known as $P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists offer significant improvements over other anti-thrombotic agents. The $P_{2T}$ receptor is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., Br. J. Pharmacology (1994), 113, 1057-1063, and Fagura et al., Br. J. Pharmacology (1998) 124, 157-164.

International Patent Applications WO 92/17488 and WO 94/18216 disclose novel $P_{2T}$ receptor antagonists and thereof, including compounds of formula (I) (see below). Compound A (a compound of formula (I) wherein $R_1$ is 3,3,3-trifluoropropyl and $R_2$ is 2-(methylthio)ethyl) is disclosed in WO 94/18216. Compound B (a compound of formula (I) wherein $R_1$ is propyl and $R_2$ is hydrogen) is disclosed in WO 92/17488.

Both compound A and compound B may be used in any condition where platelet activation or aggregation is involved. The compounds may thus act as anti-thrombotic agents and are useful in the treatment or prophylaxis of unstable angina, thromboembolic stroke and peripheral vascular disease. They may also be used in the treatment and prophylaxis of the sequalae of thrombotic complications from angioplasty, thrombolysis, endarterectomy, coronary and vascular graft surgery, renal dialysis and cardio-pulmonary bypass. In addition, they can be used in the treatment and prophylaxis of disseminated intravascular

coagulation, deep vein thrombosis, pre-eclampsia, tissue salvage following surgical or accidental trauma, vasculitis, arteritis, thrombocythaemia, ischemia and migraine.

## DISCLOSURE OF THE INVENTION

The inventors of the present invention have surprisingly found that administration of a combination of a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof, and another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, offers a significant improvement over other anti-thrombotic treatments.

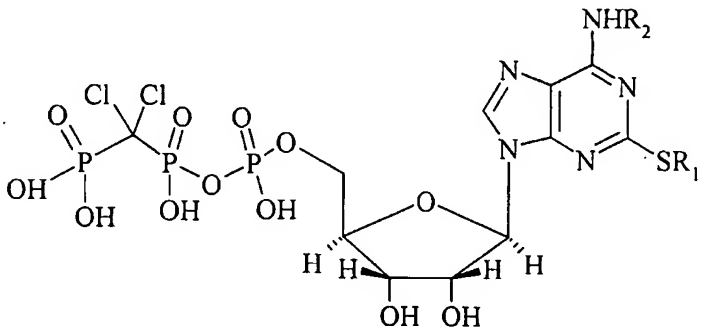
Accordingly, the combined administration of a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof and another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, can be used in the treatment and prevention of thrombosis, particularly in the treatment of the thrombotic complications of atherosclerotic disease and interventions therein.

According to a first aspect of the invention there is provided a kit of parts comprising:
(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof (component a); and
(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof (component b);
where components (a) and (b) are each provided in a form (which may be the same or different) that is suitable for administration in conjunction with each other.

Pharmaceutically acceptable derivatives of a $P_{2T}$ receptor antagonist and other anti-thrombotic agent include salts (e.g. pharmaceutically acceptable non-toxic organic or inorganic acid addition salts (such as a salt of hydrochloric, hydrobromic, nitric, sulphuric or acetic acid)), solvates and solvates of salts.

If more than one formulation comprising component (a) or component (b) is present, for example in order to provide for repeat dosing, such formulations may be the same, or may be different in terms of the dosage, chemical composition and/or physical form.

Preferably, the $P_{2T}$ receptor antagonist is the compound of formula (I):



wherein:

either $R_1$ is 3,3,3-trifluoropropyl and $R_2$ is 2-(methylthio)ethyl

or $R_1$ is propyl and $R_2$ is hydrogen;

or a pharmaceutically acceptable derivative thereof.

More preferably, the $P_{2T}$ receptor antagonist is compound A (where $R_1$ is 3,3,3-trifluoropropyl and $R_2$ is 2-(methylthio)ethyl as disclosed in WO 94/18216).

Preferably component (b) is selected from anti-platelet agents, anti-coagulant agents, fibrinolytic agents, and any combination thereof.

More preferably, component (b) is selected from the group consisting of aspirin, clopidogrel, ticlopidine, a GPIIb/IIIa antagonist, direct thrombin inhibitors, prodrugs of direct thrombin inhibitors, warfarin, heparin, low molecular weight heparins, streptokinase, tissue plasminogen activator, tenecteplase and any combination thereof. Examples of direct thrombin inhibitors include melagatran (WO 94/29336). Prodrugs of melagatran include

those described in WO 97/23499, and particularly include Example 17 of that application. Example 17 of WO 97/23499 is H 376, which is $EtO_2C$-$CH_2$-(R)Cgl-Aze-Pab-OH, wherein Cgl is cyclohexylglycinyl, Aze is (S)-azetidine-2-carbonyl and Pab is para-amidinobenzylamino and the OH replaces one of the amidino hydrogens in Pab.

In accordance with the invention, the $P_{2T}$ receptor antagonist, other anti-thrombotic agent, and derivatives of either, may be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, or via inhalation into the lung. Preferred modes of delivery are systemic. For the $P_{2T}$ receptor antagonist and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous. For the other anti-thrombotic agent and derivatives thereof, preferred modes of administration are oral or, in the case of unfractionated or low molecular weight heparins, certain direct thrombin inhibitors and fibrinolytic agents, intravenous or subcutaneous.

The sequence in which the formulations comprising the $P_{2T}$ receptor antagonist and the other anti-thrombotic agent may be administered (i.e. whether, and at what point, sequential, separate and/or simultaneous administration takes place) may be determined by the physician or skilled person. For example, the sequence may depend upon many factors, such as whether, at any time during the course or period of treatment, one or other of the formulations cannot be administered to the person for practical reasons (e.g. the person is unconscious and thus unable to take an oral formulation).

Respective formulations comprising component (a) and/or component (b) may be administered, sequentially, separately and/or simultaneously, over the course of treating the relevant condition, which condition may be acute or chronic. Preferably, the two formulations are administered (optionally repeatedly) sufficiently closely in time for there to be a beneficial effect for the patient, that is greater, over the course of the treating the relevant condition, than if either of the two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of

treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of a particular condition, will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

Alternatively, one or other of the two component formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration with the other component. Individual doses of a $P_{2T}$ receptor antagonist and other anti-thrombotic agent may be used within 48 hours (e.g. 24 hours) of each other.

In the therapeutic treatment of mammals, and especially humans, the $P_{2T}$ receptor antagonist, other anti-thrombotic agent, and derivatives of either, may be administered alone, but will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which should be selected with due regard to the intended route of administration and standard pharmaceutical practice.

In accordance with the invention, the kit of parts may be used in medical therapy, suitably in the treatment of thrombosis. The treatment of thrombosis will be understood by those skilled in the art to include the treatment and prevention of thrombotic complications of atherosclerotic disease and interventions therein, such as fibrinolysis, endarterectomy or percutaneous transluminal coronary revascularisation (PTCR), including, but not limited to, percutaneous transluminal coronary angioplasty (PTCA) with or without stenting. Thrombotic complications of atherosclerotic disease include, but are not limited to, acute coronary syndrome (encompassing acute myocardial infarction with or without ST elevation and unstable angina) and thrombotic stroke.

A further aspect of the invention provides a method of treating thrombosis (for example thrombotic complications of atherosclerotic disease and interventions therein, such as fibrinolysis, endarterectomy or percutaneous transluminal coronary revascularisation (PTCR), including, but not limited to, percutaneous transluminal coronary angioplasty (PTCA) with or without stenting) which comprises using a kit of parts for administering a

therapeutically effective amount of a $P_{2T}$ receptor and another anti-thrombotic agent to a person suffering from or susceptible to such a disorder.

For avoidance of doubt the term "treatment" includes therapeutic and/or prophylactic treatment.

Preferably component component (a) is administered parenterally prior to surgery and component (b) is administered orally following that surgery.

According to another aspect of the invention, there is provided a method of making a kit of parts as defined herein, which comprises bringing a component (a) into association with a component (b) thus rendering the two components suitable for administration in conjunction with each other. By bringing the two components into association with each other, we include that components (a) and (b) may be:

i) packaged presented and purchased as separate formulations which are subsequently used in conjunction in combination therapy; or

ii) packaged and presented together as separate components of a combination pack for use in conjunction with each other in combination therapy.

The present invention still further provides a kit of parts comprising:

(1) components (a) and (b) as defined herein; together with

(2) instructions to use the components in conjunction with each other.

The invention further provides the use of a $P_{2T}$ receptor antagonist, or a pharmaceutically acceptable derivative thereof, in the manufacture of a kit of parts for the treatment of thrombosis.

Components (a) and (b) as described herein may also be co-formulated as a combined preparation (i.e. presented as a single formulation including a $P_{2T}$ receptor antagonist and other anti-thrombotic agent).

Thus, a further aspect of the invention provides a pharmaceutical formulation comprising:
(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof; and
(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof; in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Preferably component (a) is a compound of formula (I) as defined above, or a pharmaceutically acceptable derivative thereof. Preferably component (b) is selected from anti-platelet agents, anti-coagulant agents, fibrinolytic agents, and any combination thereof. More preferably, component (b) is selected from the group consisting of aspirin, clopidogrel, ticlopidine, a GPIIb/IIIa antagonist, direct thrombin inhibitors, prodrugs of direct thrombin inhibitors, warfarin, heparin, low molecular weight heparins, tissue plasminogen activator, tenecteplase, and any combination thereof.

The present invention provides a pharmaceutical formulation comprising:
(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof; and
(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof; in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;
for use in medical therapy, suitably in the treatment of thrombosis.

The invention further provides a method of treating thrombosis which comprises administering a therapeutically effective amount of a pharmaceutical formulation comprising:
(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof; and
(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof; in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;
to a person suffering from or susceptible to such a disorder.

In another aspect of the present invention, there is provided a process for the preparation of a pharmaceutical formulation which comprises mixing a $P_{2T}$ receptor antagonist with another anti-thrombotic agent.

The invention further provides the use of a pharmaceutical formulation as hereinbefore defined in the manufacture of a medicament for the treatment of thrombosis.

Another aspect of the invention involves the use of:

(a) a pharmaceutical formulation comprising a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation comprising another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

in therapy, suitably in the treatment of thrombosis.

A further aspect of the invention provides a method of treating thrombosis which comprises administering:

a) a pharmaceutical formulation comprising a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, and

b) a pharmaceutical formulation comprising another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

to a person suffering from or susceptible to such a disorder.

In another aspect of the present invention, there is provided the use of a $P_{2T}$ receptor antagonist, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament to be used in combination with another anti-thrombotic agent in the treatment of thrombosis. Preferably the $P_{2T}$ receptor antagonist is a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

Suitable formulations for administering a $P_{2T}$ receptor antagonist are known in the art, and include those known from WO 92/17488 and WO 94/18216.

Suitable formulations for administering other anti-thrombotic agent are described in the literature, for example, when the other anti-thrombotic agent is melagatran, or a prodrug of melagatran, suitable formulations include those described in *inter alia* WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912, WO 99/27913, WO 00/13672 and WO 00/12043. Otherwise, the preparation of suitable formulations may be achieved by the skilled person using routine techniques.

Suitable doses of the $P_{2T}$ receptor antagonist, the other anti-thrombotic agent, and derivatives of either can be determined by the medical practitioner or other skilled person, and will depend on the severity of the condition, and on the person to be treated, as well as the compound(s) which is/are employed. Respective doses are discussed in the prior art documents disclosing $P_{2T}$ receptor antagonists and other anti-thrombotic agents that are mentioned hereinbefore.

In the case of a compound of formula (I), suitable doses of active compound in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 μmol/L, for example in the range 0.001 to 5 μmol/L over the course of treatment of the relevant condition. In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual person, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular person to be treated. The above-mentioned dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The pharmaceutical formulation of the invention may, and indeed will usually, contain various other ingredients known in the art, for example preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents. Thus the pharmaceutical formulation of the invention will typically comprise a total amount of (a)

the $P_{2T}$ receptor antagonist and (b) another anti-thrombotic agent (the active ingredients) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the range from 0.10 to 70 %w, and even more preferably in the range from 0.10 to 50 %w, all percentages by weight being based on total formulation.

## EXAMPLES

The invention is illustrated, but in no way limited, by the following examples, either utilising compound A (a compound of formula (I) wherein $R_1$ is 3,3,3-trifluoropropyl and $R_2$ is 2-(methylthio)ethyl) or, in Example 3, using data obtained with the close structural analogue, compound B (a compound of formula (I) wherein $R_1$ is propyl and $R_2$ is hydrogen, synthesised at AstraZeneca R & D, Charnwood, Humphries et al (1995), Br J Pharmacol., 115; 1110-1116).

### Example 1

**Canine Coronary Thrombosis Model - compound A and aspirin/heparin**

Compound A was used in combination with aspirin and unfractionated heparin in a dog model of coronary artery thrombosis to determine whether addition of a $P_{2T}$-receptor antagonist to these standard anti-platelet and anti-coagulant agents could improve coronary artery patency after thrombolysis with tPA. All animals were treated with both aspirin 325 mg and unfractionated heparin 80 U/kg then 17 U/kg/h. The test group (n = 10) was treated with compound A (4 μg/kg/min iv) from 10 min prior to tPA until end of protocol (2 h post reperfusion). The placebo group (n = 10) received only a saline infusion iv from 10 min prior to tPA until end of protocol (2 h post reperfusion).

The results of the experiments are evident in tables 1 and 2.

Coronary artery blood flow following successful thrombolysis with tPA was significantly better maintained in a group of animals receiving compound A in addition to aspirin and heparin than in a group receiving saline, aspirin and heparin (table 1).

**Table 1. Effects on coronary thrombolysis by tPA**

| Parameter | Saline | Compound A |
|---|---|---|
| Baseline blood flow (ml/min) | 65.3 ± 7.5 | 62.3 ± 8.5 ns |
| Time to occlusion (min) | 55.5 ± 14.0 | 62.3 ± 14.7ns |
| Reperfusion rate | 100% | 100%ns |
| Time to reflow (min) | 21.5 ± 2.9 | 20 ± 6.1ns |
| Reflow duration (min) | 75.0 ± 39.9 | 119.7 ± 0.7* |
| Cyclic flow variation | 50% | 0%* |
| Reocclusion | 60% | 0%* |

* $P<0.05$

Infarct size was also reduced significantly ($P < 0.05$) in animals receiving compound A (table 2). These results suggest that significant additional clinical benefit will be attained when a $P_{2T}$ antagonist is combined with a fibrinolytic agent and standard anti-platelet and anti-coagulant therapy.

**Table 2. Infarct size reduction**

| | Saline | Compound A | |
|---|---|---|---|
| Area at risk ($cm^2$) | 48.7 ±6.9 | 49.9 ± 8.4 | Ns |
| Infarct size ($cm^2$) | 9.3 ± 4.4 | 4.7 ± 4.7 | P = 0.034 |

**Example 2**

**Human blood in vitro - compound A and clopidogrel**

Compound A (500 nM final concentration) was added to blood from healthy human volunteers receiving clopidogrel (Sanofi-Winthrop, 75 mg/day for 11 days). ADP-induced platelet aggregation (+/- compound A) was measured using whole blood impedance aggregometry.

Clopidogrel alone resulted in slowly developing, incomplete inhibition of the ADP response (Table 3). Compound A added *in vitro* produced complete or near complete inhibition of the response to low to intermediate concentrations of ADP (up to 30 μM) both before and during administration of clopidogrel (data for ADP 10 μM shown in Table 3) while substantial inhibition of the response to the highest concentration of ADP used (300 μM) required a combination of both compound A and clopidogrel.

**Table 3: Effect of oral clopidogrel (75 mg/day) on ADP (10 and 300 μM)-induced platelet aggregation measured in blood from healthy human volunteers *ex vivo* (+/- compound A (500 nM) added *in vitro*)**

| Duration of clopidogrel administration (days) | Aggregation (ohms) (mean ± SD, n = 7 – 8 except where indicated) | | | |
|---|---|---|---|---|
| | ADP 10 μM | | ADP 300 μM | |
| | - compound A | + compound A | - compound A | + compound A |
| 0 | 14.9 ± 1.9 | 0.5 ± 0.7 | Not measured | 6.5 ± 3.4 |
| 1 | 13.8 ± 2.3 | 0.4 ± 0.7 | Not measured | 4.2 ± 2.6 |
| 2 | 11.8 ± 3.4 | 0.4 ± 0.6 | Not measured | 2.9 ± 2.3 |
| 3 | 10.2 ± 4.5 | 0.6 ± 0.7 | 13.9 (n=1) | 2.7 ± 2.1 |
| 11 | 8.2 ± 4.4 | 0.6 ± 0.8 | 11.4 ± 5.2 (n=3) | 2.8 ± 2.8 |

**Example 3**

P-selectin expression on the platelet membrane surface plays an important role in platelet-leukocyte-conjugate formation and there is increasing evidence that such interactions play an important role in both acute thrombosis and in the inflammatory aetiology of progressive atheroscerosis. The effect of a $P_{2T}$-receptor antagonist (compound B) on ADP (10 μM)-induced platelet P-selectin expression was investigated in human washed platelets. The effect of compound B (10 nM) was compared with that of the GPIIb/IIIa antagonist, GR144053 (10 μM, Foster et al (1993) Thromb Haemostas;69(6):559, synthesized in AstraZeneca R & D, Charnwood). These concentrations are 4 (compound B)- and 600 (GR144053)-fold higher than the respective $IC_{50}$ values for inhibition of ADP-induced platelet aggregation in this system. The results are summarised in Table 4.

**Table 4: Effect of compound B and GR144053 alone or in combination on ADP (10 μM)-induced P-selectin expression in human washed platelets**

| Conditions | P-selectin expression (% positive cells) Mean ± se (n = 3) |
|---|---|
| Control | 13.1 ± 3.3 |
| + GR144053 (10 μM) | 17.7 ± 1.7 |
| + compound B (10 nM) | 4.9 ± 2.6 |
| + GR144053 (10 μM) + compound B (10 nM) | 7.5 ± 1.6 |

The $P_{2T}$-receptor antagonist, at a concentration consistent with known effects on ADP-induced platelet aggregation, substantially inhibits ADP-induced P-selectin expression in the absence or presence of the GPIIb/IIIa antagonist. In contrast, the GPIIb/III antagonist alone had no effect on P-selectin expression at a concentration considerably in excess of that which would completely inhibit platelet aggregation. These results suggest the potential for combination therapy with GPIIb/IIIa antagonists and $P_{2T}$-receptor antagonists, wherein the broad-spectrum anti-aggregatory effect of the former class is complemented by the additional effect of the latter on other aspects of platelet activation, such as pro-inflammatory P-selectin expression.

**Abbreviations**

ADP = adenosine diphosphate

GPIIb/IIIa antagonist = glycoprotein IIb/IIIa antagonist

PTCR = percutaneous transluminal coronary revascularisation

PTCA = percutaneous transluminal coronary angioplasty

TIMI = thrombolysis in myocardial infarction

tPA = tissue plasminogen activator

**Claims**

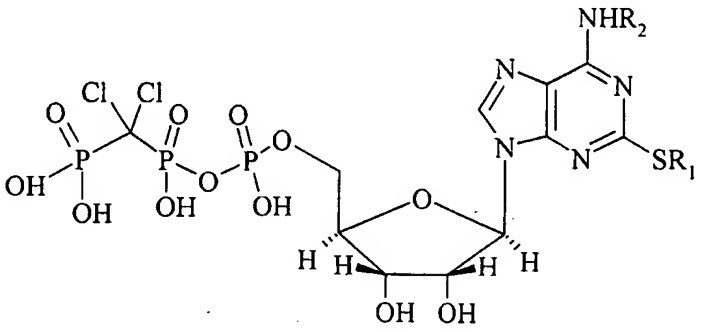
1. A kit of parts comprising:

(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof (component a); and

(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof (component b);

where components (a) and (b) are each provided in a form (which may be the same or different) that is suitable for administration in conjunction with each other.

2. A kit of parts according to claim 1, wherein component (a) is a compound of formula (I):



wherein:

either $R_1$ is 3,3,3-trifluoropropyl and $R_2$ is 2-(methylthio)ethyl

or $R_1$ is propyl and $R_2$ is hydrogen,

or a pharmaceutically acceptable derivative thereof.

3. A kit of parts according to claim 1 or 2, wherein the anti-thrombotic agent is selected from anti-platelet agents, anti-coagulant agents, fibrinolytic agents, and any combination thereof.

4. A kit of parts according to any one of claims 1 to 3, wherein the anti-thrombotic agent is selected from the group consisting of aspirin, clopidogrel, ticlopidine, a GPIIb/IIIa

antagonist, direct thrombin inhibitors, prodrugs of direct thrombin inhibitors, warfarin, heparin, low molecular weight heparins, tissue plasminogen activator, tenecteplase, and any combination thereof.

5. A kit of parts according to any one of claims 1 to 4, wherein the anti-thrombotic agent is a direct thrombin inhibitor and/or a prodrug of a direct thrombin inhibitor.

6. A kit of parts as claimed in claim 5, wherein the thrombin inhibitor is melagatran.

7. A kit of parts as claimed in claim 5, wherein the prodrug of melagatran is $EtO_2C$-$CH_2$-(R)Cgl-Aze-Pab-OH

8. A kit of parts according to any one of claims 1 to 7, wherein components (a) and (b) are suitable for sequential, separate and/or simultaneous administration.

9. A kit of parts according to any one of claims 1 to 7, for use in medical therapy.

10. A kit of parts according to any one of claims 1 to 7, for use in the treatment of thrombosis.

11. A method of treating thrombosis which comprises using a kit of parts according to any one of claims 1 to 7, for administering a therapeutically effective amount of a $P_{2T}$ receptor and another anti-thrombotic agent to a person suffering from or susceptible to such a disorder.

12. A method according to claim 11, wherein component (a) is administered parenterally prior to surgery and component (b) is administered orally following that surgery.

13. The use of a $P_{2T}$ receptor antagonist according to any one of claims 1 to 12, or a pharmaceutically acceptable derivative thereof, in the manufacture of a kit of parts for the treatment of thrombosis.

14. A pharmaceutical formulation comprising:

(a) a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof; and

(b) another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof;

in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

15. A pharmaceutical formulation according to claim 14, wherein the $P_{2T}$ receptor antagonist is a compound of formula (I) as defined in claim 2, or a pharmaceutically acceptable derivative thereof.

16. A pharmaceutical formulation according to claim 14 or 15, wherein the anti-thrombotic agent is selected from anti-platelet agents, anti-coagulant agents, fibrinolytic agents, and any combination thereof.

17. A pharmaceutical formulation according to any one of claims 14 to 16, wherein the anti-thrombotic agent is selected from the group consisting of aspirin, clopidogrel, ticlopidine, a GPIIb/IIIa antagonist, direct thrombin inhibitors, prodrugs of direct thrombin inhibitors, warfarin, heparin, low molecular weight heparins, tissue plasminogen activator, tenecteplase, and any combination thereof.

18. A pharmaceutical formulation according to any one of claims 14 to 17, wherein the anti-thrombotic agent is a direct thrombin inhibitor and/or a prodrug of a direct thrombin inhibitor.

19. A pharmaceutical formulation according to claim 18, wherein the thrombin inhibitor is melagatran.

20. A pharmaceutical formulation according to claim 18, wherein the prodrug of melagatran is $EtO_2C$-$CH_2$-(R)Cgl-Aze-Pab-OH

21. A pharmaceutical formulation according to any one of claims 14 to 20 for use in medical therapy.

22. A pharmaceutical formulation according to any one of claims 14 to 20 for use in the treatment of thrombosis.

23. The use of a pharmaceutical formulation according to any one of claims 14 to 20 in the manufacture of a medicament for the treatment of thrombosis.

24. A method of treating thrombosis which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 14 to 20 to a person suffering from or susceptible to such a disorder.

25. A process for the preparation of a pharmaceutical formulation according to any one of claims 14 to 20 which comprises mixing a $P_{2T}$ receptor antagonist with another anti-thrombotic agent.

26. The use of:
(a) a pharmaceutical formulation comprising a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
(b) a pharmaceutical formulation comprising another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
in therapy.

27. The use of:
(a) a pharmaceutical formulation comprising a $P_{2T}$ receptor antagonist or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation comprising another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
in the treatment of thrombosis

28. The use of a pharmaceutical formulation according to claims 26 or 27, wherein the $P_{2T}$ receptor antagonist is a compound of formula (I) as defined in claim 2.

29. A method of treating thrombosis which comprises administering to a person suffering from, or susceptible to such a condition:
(a) a pharmaceutical formulation comprising a $P_{2T}$ receptor antagonist, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, and
(b) a pharmaceutical formulation comprising another anti-thrombotic agent or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

30. A method according to claim 29, wherein the $P_{2T}$ receptor antagonist is a compound of formula (I) as defined in claim 2.

31. A method according to claim 29 or 30, wherein the anti-thrombotic agent is selected from anti-platelet agents, anti-coagulant agents, and any combination thereof.

32. A method according to any one of claims 29 to 31, wherein the anti-thrombotic agent is selected from the group consisting of aspirin, clopidogrel, ticlopidine, a GPIIb/IIIa antagonist, direct thrombin inhibitors, prodrugs of direct thrombin inhibitors, warfarin, heparin, low molecular weight heparins, tissue plasminogen activator, tenecteplase, and any combination thereof.

33. A method according to any one of claims 29 to 32, wherein the anti-thrombotic agent is a direct thrombin inhibitor and/or a prodrug of a direct thrombin inhibitor.

34. A method according to claim 33, wherein the thrombin inhibitor is melagatran.

35. A method according to claim 33, wherein the prodrug of melagatran is $EtO_2C$-$CH_2$-(R)Cgl-Aze-Pab-OH

36. A method according to any one of claims 29 to 35, wherein component (a) is a parenteral formulation and component (b) is an oral formulation.

37. A method according to any one of claims 29 to 36, wherein component (a) is administered parenterally prior to surgery and component (b) is administered orally following that surgery.

38. The use of a $P_{2T}$ receptor antagonist, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament to be used in combination with another anti-thrombotic agent in the treatment of thrombosis

39. The use of a compound of formula (I) as defined in claim 2, or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament to be used in combination with another anti-thrombotic agent in the treatment of thrombosis.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02378

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/7076, A61K 31/727, A61P 7/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI, CAPLUS, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | Current Opinionin Cardiovascular, Pulmonary & Renal Investigational Drugs vol. 1, no. 5, 1999, Ann Arbor: "AR-C69931MX AstraZeneca Sarat CChattaraj", page 600 - page 604 --- | 1-39 |
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 March 2001 | 14 -03- 2001 |
| Name and mailing address of the ISA<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Eva Johansson/EÖ<br>Telephone No. +46 8 782 25 00 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02378

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | J. Med. Chem., Volume 42, 1999, Anthony H. Ingall et al, "Antagonists of the Platelet P2T Receptro. A Novel Approach to Antithrombotic Therapy" page 213 - page 220 -- | 1-39 |
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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02378

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11,12,24, 26-37
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02378

Claims 11, 12, 24, 26-37 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02378

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Information on patent family members

25/02/01

International application No.
PCT/SE 00/02378

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